# Epitomes

## Important Advances in Clinical Medicine


# Neurology

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.*


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## Neurologic Consequences of Designer Drugs

WHAT ARE "designer drugs"? Most simply put, they are analogs of controlled substances (or CSAs, as we now call them). Historically, they can be viewed as the penultimate result of the synthetic drug revolution that began in the 1960s with LSD and phencyclidine hydrochloride (PCP). These new compounds are legal to possess, cheap to produce and do not have to be imported. The subject is a timely one in view of current efforts to stem the flow of illicit narcotics into the United States. If successful, this well-intended effort is likely to result in an explosion of domestically produced "synthetics." These compounds can be sold under almost any guise, including heroin, cocaine and even as marijuana (parsley laced with PCP).

There are three reasons why physicians should be concerned. Some of these compounds are extraordinarily potent, increasing the risk of overdose, particularly in the hands of a novice. One of the fentanyl analogs sold on the street, for example, is known to be 1,000 times more potent than morphine. Second, to the best of my knowledge, none of the "kitchen chemists" has ever been credited with testing a newly synthesized product on laboratory animals before releasing it for human consumption. Hence, the danger that a new toxin may "hit the street" is ever constant. Finally, quality controls are lacking. Bad batches are usually first discovered when addicts get sick.

Given the foregoing, it is not surprising that CSAs have spawned a rapidly developing branch of neurotoxicology. The first selective neurotoxin sold in California as heroin was 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (now widely known as MPTP), which appeared on the streets in 1982. MPTP selectively destroys the zona compacta of the substantia nigra and causes parkinsonism in its victims. Although there are only seven known severely involved patients with MPTP-induced parkinsonism, epidemiologic evidence suggests that more than 500 young addicts may have injected MPTP under the impression it was heroin. Hence, MPTP-induced parkinsonism should be considered in the differential diagnosis of any person with an early case of parkinsonism and a history of drug abuse.

Parkinsonism is not the only neurologic complication to result from the increasing flow of synthetic street drugs. In the past six months more than 20 cases of chorea of varying duration have been identified in persons abusing amphetamine. While amphetamine-induced chorea has been reported previously, it is rare, and the sudden appearance of a number of new cases has raised concern that a much more potent, new "designer" amphetamine may have appeared on the drug scene. Efforts are currently under way to further characterize this syndrome and identify the offending agent. For the moment, however, the acute onset of chorea in young adults should at least raise the question of amphetamine-analog abuse.

There are other analogs of amphetamine that may be equally worrisome. Methamphetamine, MDA (3,4-methylenedioxyamphetamine) and MDMA (3,4-methylenedioxymethamphetamine; "ecstasy") appear to be neurotoxic, causing prolonged depletion of serotonin and nerve terminal degeneration in the striatum and hippocampus of laboratory animals. While the clinical implications of these effects have yet to be determined, these observations provide one more cause for concern regarding the effects of synthetic drug abuse.

If there is a message in all of this, it is that physicians need to be increasingly aware of the medical hazards of the synthetic drug revolution that appears to be rapidly descending on us.


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## Immunotherapy in Multiple Sclerosis

MULTIPLE SCLEROSIS remains a disorder of unknown pathogenesis despite decades of research. Current immunologic studies imply both humoral and cellular immune dysfunction. These findings have raised the possibility of an autoimmune basis for this disease, but conclusive proof is lacking. The presumed immune dysfunction, however, forms the basis for

various currently available immunotherapies. The following treatments are now accepted in clinical practice, but should be undertaken with the guidance of a neurologist familiar with the use, risks and side effects of these methods.

*Cyclophosphamide*

During the past five years, several studies have investigated intensive immunosuppressive treatment with cyclophosphamide in patients with multiple sclerosis. Initial trials showed that about 75% of patients with chronic progressive disease received benefit defined as stabilization or abatement of clinical symptoms for a year. A recent five-year follow-up of 188 patients who received cyclophosphamide treatment showed reprogression in 87%, necessitating retreatment. The most recent treatment programs now involve an induction regimen followed by periodic outpatient booster injections of cyclophosphamide to maintain remission.

*Corticosteroids*

Long a mainstay in treating patients with relapsing or remitting multiple sclerosis, corticosteroids have shown efficacy in a new double-blind trial of high doses of parenterally administered methylprednisolone sodium succinate. The drug was administered intravenously in an initial dose of 15 mg per kg per day, tapering to 1 mg per kg per day in 15 days, followed by a course of prednisone given orally in decreasing doses over four months. Treatment with methylprednisolone was associated with significantly greater improvement and a shorter relapse duration than in control patients.

*Azathioprine*

Prolonged administration of azathioprine has been used in cases of nonremitting multiple sclerosis since the 1970s. The results of clinical trials have been mixed. Some of the studies were uncontrolled, making interpretation difficult. The combined use of azathioprine and methylprednisolone may slow the progression of the disease, according to a new three-year study conducted at UCLA. Side effects of azathioprine use include leukopenia and liver function abnormalities in some patients.

*Plasmapheresis or Lymphocytapheresis*

Reports that humoral and cellular factors may be involved in multiple sclerosis have resulted in trials of plasmapheresis and lymphocytapheresis. Previous studies of plasmapheresis have given mixed results, and some studies have combined the use of plasmapheresis with a regimen of prednisone given orally and cyclophosphamide. A multicenter, double-blind study of plasmapheresis and immunosuppression will be completed this year. Lymphocytapheresis as a long-range therapy has been tested in a one-year trial and has shown no clear benefit. As of this writing, there are insufficient data to recommend these two therapies in patients with multiple sclerosis.

*Treatments Under Investigation*

In the opinion of some experts on multiple sclerosis, patients should not be treated with investigational drugs outside of experimental protocols. A number of treatment regimens are currently under investigation and these include natural and recombinant interferon, cyclosporine, monoclonal antibodies against T-lymphocytes and poly-ICLC, a potent interferon inducer.

In summary, a number of immunotherapies are currently available or under investigation for multiple sclerosis, but the risks, side effects and benefits of these treatment measures should be carefully weighed in each case with guidance from a neurologist familiar with the treatment of this disorder.

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## Pseudoseizures

PSEUDOSEIZURES are characterized by paroxysmal behavioral alterations that may resemble epileptic seizures. Impaired responsiveness to external or internal stimuli (or both) and involuntary movements, often dramatic, are common features. Pseudoseizures are often a conversion symptom ("hysterical seizures") and may coexist with other neurologic or nonneurologic illnesses. In addition to epileptic seizures, other neurologic disorders, such as narcolepsy and migraine, or certain cardiovascular and systemic conditions, particularly syncope, must be excluded before pseudoseizures are considered. Further, the relationship between pseudoseizures and psychiatric illnesses has been poorly defined.

Because patients are rarely examined during an actual attack and are often amnestic of the ictal events, the diagnosis of pseudoseizures is taxing to a clinician. In an atmosphere of defensive medicine, practitioners are more inclined to initiate antiepileptic drug treatment than to resort to further observation when diagnostic tests are negative and the question cannot be resolved. Because of the chronicity of epilepsy that they mimic, pseudoseizures often become a chronic, disabling illness. It has been shown that a significant number of epilepsy victims also have pseudoseizures. Consideration of this disorder is important in managing epileptic seizures not only at the onset but also in refractory cases. Antiepileptic drug intoxication may aggravate pseudoseizures.

The diagnosis of pseudoseizures owes much to the increased accuracy in diagnosing epileptic seizures. It is now feasible to extend an electroencephalographic (EEG) monitor to critically examine a clinical attack. In many instances, an ambulatory cassette EEG monitor may be preferable because it does not require hospital admission. This method, however, cannot provide reliable information concerning the ictal behavior. Prolonged monitoring and documentation of a patient's behavior can only be accomplished in a hospital setting, most commonly in conjunction with a video monitor system. EEG and video data can be played back later simultaneously for detailed analysis. Such an approach is considered essential in diagnosing pseudoseizures in patients who also suffer genuine epileptic seizures.

One must realize in this diagnostic undertaking that an absence of abnormalities, even when monitoring is prolonged, does not by itself establish a diagnosis of pseudoseizures. Inducing an attack by suggestion or in a specific provocative environment is an effective means of aiding the investigation. The precipitation of genuine epileptic seizures under certain controlled circumstances, however, including